DIALKYLAMINOMETHYLNAPHTHOLS AND THEIR DERIVATIVES

BY

GERALD FRANCIS GRILLOT

B. A., Ohio State University, 1936

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE SCHOOL OF THE
UNIVERSITY OF ILLINOIS, 1940

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Introduction

An ideal local anesthetic would be one which is therapeutically active both topically and subcutaneously. It should also have a low toxicity and be non-irritating to the tissues. In spite of the fact that a tremendous number of compounds have been synthesized in an effort to find a good local anaesthetic none has as yet been obtained which possess all the desirable properties.

On 1906 Auwer and Dombrowski discovered that phenols could react with formaldehyde and secondary amines to produce dialkylaminomethylphenols. The purpose of this present work was to apply this reaction to 1- and 2-naphthols in order to obtain the dialkylaminomethylnaphthols. If a procedure could be developed for producing these compounds in high yields, then they could serve as starting materials for preparing esters such as benzoates and *p*-aminobenzoates. The latter could be obtained by treating the substituted naphthols with *p*-nitrobenzoyl chloride followed by reduction. These esters should be of considerable pharmacological interest.

Experimental

Dialkylaminomethylnaphthols:—The general method for the preparation of these compounds involved the addition of one equivalent of the amine to one equivalent of 40% formalin. A solution of eight-tenths equivalent of the naphthol which had been dissolved in alcohol was added to the above mixture. The amino-naphthol crystallized in a short time and was removed by filtration. It was then recrystallized from alcohol. In this manner 2-piperidinomethyl-1-naphthol, 1-piperidinomethyl-2-naphthol, 2-morpholinomethyl-1-naphthol and 1-morpholinomethyl-2-naphthol were prepared.

p-Nitrobenzoates:—The *p*-nitrobenzoates of the above napthols were prepared by the following method:

A solution of 15g. of the substituted naphthol, dissolved in 100c.c. of warm dry toluene, was added to 11.5g. of *p*-nitrobenzoyl

chloride dissolved in 100c.c. of warm dry toluene. The mixture was then heated for five hours on the steam cone. The solid was filtered, dried and recrystallized from alcohol.

p-Aminobenzoates:—The *p*-nitrobenzoate esters were reduced to the *p*-aminobenzoate esters as follows:

A solution of ten grams of the *p*-nitrobenzoyl esters dissolved in 250 c.c. of alcohol, in which 0.2 g. of platinum catalyst was suspended, was shaken with hydrogen which was at a pressure of three atmospheres. When six atoms of hydrogen had been absorbed the platinum was removed by filtration. The *p*-aminobenzoyl esters were obtained by evaporating the alcohol. The resulting product was recrystallized from alcohol.

Summary

2-Piperidinomethyl-1-naphthol and 1-piperidinomethyl-2-naphthol were prepared by condensing piperidine and formaldehyde with 1- and 2-naphthol, respectively. These aminonaphthols were then converted to the hydrochloride salts of the *p*-nitrobenzoyl esters. Catalytic reduction of these esters in the presence of platinum yielded 2-piperidinomethyl-1-naphthyl-*p*-aminobenzoate hydrochloride and 1-piperidinomethyl-2-naphthyl-*p*-aminobenzoate hydrochloride.

Morpholine and formaldehyde were condensed with 1- and 2-naphthol to give 2-morpholinomethyl-1-naphthol and 1-morpholinomethyl-2-naphthol, respectively. Treatment with *p*-nitrobenzoyl chloride converted these compounds to the hydrochloride salts of the *p*-nitrobenzoyl esters. These esters were then reduced catalytically to 2-morpholinomethyl-1-naphthyl-*p*-aminobenzoate hydrochloride and 1-morpholinomethyl-2-naphthyl-*p*-aminobenzoate hydrochloride.

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ADDENDUM
SYNTHESIS OF
4-METHOXYCYCLOHEXYLIDENEACETIC ACID

Introduction

In 1890 Hantzsch and Schultze observed that primary and secondary nitro compounds existed in two tautomeric forms. The one form was designated as the normal form and the other as the *aci*-form. It was then observed that the optically active nitro compounds still retain their activity when they are converted to the sodium salts of the *aci*-form. The structure suggested for the *aci*-form had to be discarded since it had a plane of symmetry. Kuhn then suggested another structure in which the carbon atom retains its asymmetry.

The purpose of the present work was to synthesize and resolve 4-methoxycyclohexylideneacetic acid, convert it to the ethyl ester of 4-nitrocyclohexylideneacetic acid and determine whether the sodium salt of this nitro compound retained its optical activity.

Discussion of Results

The method used for the synthesis of 4-methoxycyclohexylideneacetic acid involved the following sequence of compounds:

Hydroquinone → 4-Methoxyphenol → 4-Methoxycyclohexanol → 4-Methoxycyclohexanone → Ethyl 1-hydroxy-4-methoxy-1-cyclohexylacetate → 1-Hydroxy-4-methoxy-1-cyclohexylacetic acid → 4-Methoxycyclohexylideneacetic acid.

The monomethyl ether of hydroquinone was produced in yields of 55 percent by treating hydroquinone with sodium hydroxide and methyl sulfate. This monomethyl ether was reduced with hydrogen under pressure, using Raney Nickel as a catalyst to give a 45 percent yield of 4-methoxycyclohexanol. 4-Methoxycyclohexanol was oxidized with chromic acid solution to give 4-methoxycyclohexanone.

Ethyl 1-hydroxy-1-cyclohexylacetate was prepared in a yield of 56 per cent by condensing cyclohexanone with ethyl bromoacetate in the presence of zinc. Dehydration of this ester with potassium acid sulfate gave ethyl Δ'-cyclohexeneacetate. This ester could be saponified to Δ'-cyclohexeneacetic acid.

Cyclohexanolacetic acid was prepared by saponifying ethyl 1-hydroxy-1-cyclohexylacetate. When heated with acetic anhydride it lost water to form cyclohexylideneacetic acid in a 50 percent yield.

Ethyl 1-hydroxy-4-methoxy-1-cyclohexylacetate was prepared in a yield of 55 per cent by condensing 4-methoxycyclohexanone with ethyl bromoacetate in the presence of zinc. The acid was prepared from the ester by saponifying with caustic potash. 4-Methoxycyclohexylideneacetic acid was prepared by dehydrating 1-hydroxy-4-methoxy-1-cyclohexylacetic acid with acetic anhydride.

VITA

The writer was born in Versailles, Ohio on January 24, 1914. He attended the parochial school from 1920 to 1928. He graduated from Versailles High School in June, 1932. He attended Ohio State University from September, 1932 to June, 1936 and was granted the degree of Bachelor of Arts. He entered the Graduate School of the University of Illinois in September, 1936. He served as an assistant in the Chemistry Department of the University of Illinois during the years from September, 1936 to June, 1940.